Docket No.: 49663(48340)
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Heather J. Belmont *et al.*

Application No.: 10/024,648 | Confirmation No.: 2636

Filed: December 19, 2001 | Art Unit: 1633

For: TRANSGENIC ANIMALS COMPRISING A HUMANIZED IMMUNE SYSTEM | Examiner: A. M. S. Wehbe

AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. 1.116

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir/Madam:

INTRODUCTORY COMMENTS

Further to the Notice of Appeal, which was filed on September 29, 2010, and in lieu of an Appeal Brief, Applicants submit this paper concurrently with a Request for Continued Examination together with a Request for a one-month Extension of Time, and the requisite fee. Before the mailing of an action on the merits, Applicants respectfully request an interview with the Examiner and her supervisor.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 7 of this paper.

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A non-human transgenic animal capable of producing heterologous T-cell receptors with a substantial T-cell receptor repertoire, comprising:

inactivated endogenous T-cell receptor loci; and

transgenes contained within its genome composed of unrearranged human T-cell receptor alpha and beta loci, wherein expression of the transgenes is controlled by human T-cell receptor loci regulatory sequences and wherein said animal is capable of productive rearrangement of the human T-cell receptor alpha and beta loci to encode functional heterologous T-cell receptors.

2. (Original) The non-human transgenic animal of claim 1, wherein said inactivated endogenous T-cell receptor loci are α and ß chain T-cell receptor loci.

3. (Cancelled)

4. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said human T-cell receptor loci are composed, in operable linkage, of a plurality of human T-cell receptor V genes, and D and /or J and C genes.

5. (Previously Presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is capable of productive VDJC rearrangement and is capable of expressing heterologous T-cell receptors.

6. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said transgenes undergo productive VDJC rearrangement in lymphocytes of said nonhuman transgenic animal and wherein T-cells express detectable amounts of transgenic TCR in response to antigenic stimulation.

7. (Previously presented) The non-human transgenic animal as in one of claims 1-2 wherein said non-human transgenic animal produces an immune response to an antigen, said immune response comprising a population of T-cells reactive to an antigen and wherein the T-cell receptors comprise a human T-cell receptor.

8 – 29. (Cancelled)

30. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is any animal which can be manipulated transgenically.

31. (Previously presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is a mouse.

32 – 37. (Cancelled)

38. (Currently amended) A method of producing a non-human transgenic animal capable of productive rearrangement of the human T-cell receptor α and ß loci and of producing heterologous T-cell receptors with a substantial T-cell receptor repertoire, comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell;

inserting transgenes containing active, unrearranged α and ß chain human T-cell receptor loci in said embryo or embryonic stem cell, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene wherein the animal is capable of producing T-cells that express functional heterologous human T-cell receptors; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

39. (Original) The method of claim 38 wherein said endogenous T-cell receptor loci are α and ß chain T-cell receptor loci.

40. (Cancelled)

41. (Currently amended) A method of producing a non-human transgenic animal capable of productive rearrangement of the human T-cell receptor α and ß loci and of producing heterologous T-cell receptors with a substantial T-cell receptor repertoire, comprising the steps of:

inactivating endogenous T-cell receptor loci in an embryo or embryonic stem cell, wherein said loci are T-cell receptor α or T-cell receptor ß loci;

producing a transgenic animal from said embryo or embryonic stem cell which contains inactivated loci wherein the animal is incapable of expressing said endogenous loci;

crossing a produced transgenic animal having inactivated endogenous T-cell receptor α loci with a produced transgenic animal having inactivated endogenous T-cell receptor ß loci;

selecting progeny having both inactivated endogenous T-cell receptor α and T-cell receptor ß loci;

inserting transgenes containing active, unrearranged human T-cell receptor loci in an embryo or embryonic stem cell wherein said human T-cell receptor loci are human T-cell receptor α or T-cell receptor ß loci, wherein expression of the transgenes is controlled by T-cell receptor loci regulatory sequences;

producing a transgenic animal from said embryo or embryonic stem cell which contains the active human transgene;

crossing a produced transgenic animal having active human T-cell receptor α transgenes with produced transgenic animal having active human T-cell receptor ß transgenes;

selecting progeny having both active human T-cell receptor α and T-cell receptor ß transgenes wherein the animal is capable of producing T-cells that express functional heterologous human T-cell receptors;

crossing a produced transgenic animal having both inactivated endogenous T-cell receptor α and T-cell receptor ß loci with a produced transgenic animal having both active human T-cell receptor α and T-cell receptor ß transgenes;

selecting progeny having inactivated endogenous T-cell receptor α and T-cell receptor ß loci and containing active human T-cell receptor α and T-cell receptor ß-transgenes; and

breeding the transgenic animal as needed to produce the transgenic animal and its progeny capable of producing heterologous T-cell receptors.

42. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by a functional limitation of the loci.

43. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by deleting J segment genes from said loci.

44. (Previously presented) The method as in one of claims 38, 39, 41 wherein said

endogenous T-cell receptor loci are inactivated by deleting D segment genes from said loci.

45. (Previously presented) The method as in one of claims 38, 39, 41 wherein said endogenous T-cell receptor loci are inactivated by deleting C segment genes from said loci.

46. (Cancelled)

47. (Previously Presented) The method as in one of claims 38, 39, 41 wherein said transgenes containing the active human T-cell receptor loci comprise, in operable linkage, a plurality of human T-cell receptor V genes, and D and/or J and C genes.

48 — 111. (Cancelled)

112. (Currently amended) A non-human transgenic animal comprising inactivated endogenous T-cell receptor gene loci, said transgenic animal further containing in its genome transgenes composed of unrearranged human T-cell receptor α and ß loci, comprising, in operable linkage, a plurality of human T-cell receptor V genes, and their D and /or J and C genes, wherein said animal is capable of productive rearrangement of the human T-cell receptor alpha and beta loci to encode functional heterologous T-cell receptors with a substantial T-cell receptor repertoire.

113. (Previously Presented) A non-human transgenic animal having a germline genome with:

a human T-cell receptor ß chain transgene comprising in operable linkage a plurality of human V genes, and either one or both of the C ß loci and wherein in lymphocytes of said non-human transgenic animal the human T-cell receptor ß chain transgene undergoes productive VDJ rearrangement and produces T-cells expressing TCR human ß chain in detectable amounts in response to antigenic stimulation;

a human T-cell receptor α chain transgene with plurality of human V gene segments, human J gene segments, the human C α coding exon, and a human 3' downstream α-enhancer; and wherein in lymphocytes of said non-human transgenic animal the human T-cell receptor α chain transgene undergoes productive VJ rearrangement and produces T-cells expressing TCR human α-chain in detectable amounts in response to antigenic stimulation;

an endogenous TCR ß chain loci having an inactivated ß chain gene;

and an endogenous TCR α chain loci having an inactivated α chain gene.

114. (Previously Presented) The non-human transgenic animal of claim 1 or 2, wherein the human TCR α locus contains all of the human TCR α V region, J region and C region genes.

115. (Previously Presented) The non-human transgenic animal of claim 114, wherein the human TCR ß locus contains all of the human TCR ß V region, D region, J region and C region genes.

116. (Previously Presented) The non-human transgenic animal as in one of claims 1-2, wherein said animal is capable of producing a repertoire of functional heterologous TCRs.

117. (Previously Presented) The non-human transgenic animal of claim 5, wherein expression of the heterologous T-cell receptors is necessary for T-cell development, T-cell maturation or antigen stimulated responses.

118. (Previously Presented) The non-human transgenic animal of claim 5, wherein the heterologous T-cell receptors are expressed on pre-T cells so to effect T-cell development, produce mature, functional T-cells, or elicit an effective antigen-stimulated response.

REMARKS

Claims 1, 2, 4-7, 30, 31, 38, 39, 41-45, 47, and 112-118 are pending and under examination. Claims 1, 38, 41, and 112 have been amended. Support for the amendments can be found in paragraph [0119] of the specification. Accordingly, no new matter has been added.

Interview Summary

Applicants thank the Examiner for the interview of June 29, 2010. As reflected in the Interview Summary dated June 30, 2010, the Examiner suggested adding language to the claims regarding the repertoire of human TCRs present in the transgenic mice. As discussed below in the context of the rejections under 35 U.S.C. § 103, Applicants have amended the claims as suggested by the Examiner.

Rejections under 35 U.S.C. § 103

Claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-113 and 116-118 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240.

Claims 114-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al. (1997) Blood, Vol. 90(3), 1233-1240 as applied to claims 1-2, 4-7, 30-31, 38-39, 41-47, 112-113, and 116-118 above, and further in view of the NCBI database Accession Number NG 001332.

In the sake of brevity, Applicants will address both rejections together. For all the reasons presented in all the prior responses, Applicants respectfully disagree with the rejections. Nevertheless, without acquiescing with the rejection and solely to facilitate prosecution and allowance, Applicants have amended claims 1, 38, 41, and 112 as suggested by the Examiner during the June 29, 2010 interview. As amended, the claims are directed to a transgenic mouse

capable of producing heterologous T-cell receptors with a substantial T-cell receptor repertoire. None of the cited references, either individually or in combination teach or suggest a transgenic mouse capable of producing heterologous T-cell receptors with a substantial T-cell receptor repertoire. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Applicant hereby authorizes the Commissioner to charge Deposit Account No. 04-1105 the fee for a one-month extension of time for response, small entity, referencing Docket No. 49663(48340).

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: December 21, 2010

Respectfully submitted,
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